UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/670,096 | 09/26/2000 | Linda S. Mansfield | MSU 4.1-526 | 7494 |

21036 7590 10/18/2007

MCLEOD & MOYNE, P.C.
2190 COMMONS PARKWAY
OKEMOS, MI 48864

| EXAMINER | |
|---|---|
| BASKAR, PADMAVATHI | |
| **ART UNIT** | **PAPER NUMBER** |
| 1645 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 10/18/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov



**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 09/670,096
Filing Date: September 26, 2000
Appellant(s): MANSFIELD ET AL.

Ian McLeod
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 5/29/07 appealing from the Office action mailed 12/27/06.

***(1) Real Party in Interest***

A statement identifying the real party in interest is contained in the brief.

***(2) Related Appeals and Interferences***

A statement identifying the related appeals and interferences, which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

***(3) Status of Claims***

The statement of the status of the claims contained in the brief is correct.

***(4) Status of Amendments After Final***

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

***(5) Summary of Invention***

The summary of invention contained in the brief is correct.

***(6) Issues***

The appellant's statement of the issues in the brief is correct.

***(7) Claims Appealed***

The copy of the appealed claims contained in the Appendix to the brief is correct.

***(8) Prior Art of Record***

Liang et al 1997 Analytical Biochemistry; 250 (1) 61-5.

Liang et al 1998 Infection and Immunity; 66 (5) 1834-1838.

Harlow and Lane 1988, Chapter 6, Antibodies; Cold Spring Harbor.

***(9) Grounds of Rejection***

The following ground(s) of rejection are applicable to the appealed claims: This rejection is set forth in prior Office Actions, Final Rejection, mailed on 12/27/06 and Advisory Action, mailed on 4/9/07.

Claims 21 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liang et al 1998 (Infection and Immunity; 66 (5) 1834-1838) and Liang et al 1997 (Analytical Biochemistry; 250 (1) 61-5) each in view of Harlow and Lane 1988 (IDS: Antibodies; especially chapter 5 and 6 Cold Spring Harbor).

Claims are drawn to a method for treating an equid infected with *S.neurona* comprising: (a) providing a mixture of antibodies against a 16 kD antigen and a 30 kD antigen, both of which are specific to *S. neurona*, wherein the antibodies are selected from the group consisting of polyclonal antibodies from serum from an animal immunized with the antigen and monoclonal antibodies from a hybridoma, and wherein the antibodies are in a pharmaceutically acceptable carrier; and (b) inoculating the equid with the antibodies in the carrier to treat the equid.

Liang et al 1998 teach a method of inhibiting merozoite activity (page 1835, right column, second para through 1836, left column) comprising providing a mixture of antibodies obtained from equine serum and cerebrospinal fluid (CSF) samples including samples from horses with neurologic signs typical of EPM (equine protozoal myeloencephalitis) and identified four band patterns. The four-immunoblot patterns group 1, N1-N7 (CSF from EPM) ; group 2, 31-34; group 3, 41-46; and group 4, 51-56 ( groups 2-4 are serum from *S.neurona* infected horses ) based on the combinations of Sn 30, 16, 14 and 11 (30KD, 16KD, 14KD and 11KD respectively) proteins as represented in Figures 1 and 2. As shown in Figure 3, the intensity of 30KD, 16KD, and 14KD antigens was greatly reduced after treatment with trypsin indicating that these proteins are surface proteins of merozoites and were accessible to the action of enzyme. The prior art identified 30KD, 16KD, 14KD and 11 KD antigens from serum samples as cell surface antigens of merozoites . A combination of the results of western-blot analysis (figure 1) and trypsin digestion (figure 3 B) suggests that these are important surface proteins that could be used in specific diagnosis of *S.neurona* infection, as candidate antigens for vaccine development and specific antibodies to these antigens lyse merozoites via complement or inhibit their attachment and penetration to host cells (see abstract, figure 1& figure 3 B). Further, the prior art suggests that monoclonal antibodies are often used to study parasitic proteins and combination of techniques including western-blot analysis (figure 1) and trypsin

digestion has been shown to be effective in the identification of mixture of specific surface antigens (page 1837, right column, first and second paragraphs). *S.neurona* infection in horses induced a mixture of antibodies including 16 KD and 30 KD antigens indicating that these proteins are strong immunogens. Serum and CSF samples comprised mixture of antibodies to including 16KD and 30KD antigens. Correlation of band pattern with inhibitory activity indicated that there is correlation with 16KD and 30 KD antigens and neutralization ( lysing the merozoites in *vitro* ) assays (see page 1836 figure 2, results summarized in groups 2, 3 and 4) using said mixture of antibodies, obtained from serum samples. However, 30KD antigen was recognized in immunoblot assays but no inhibitory activity was correlated *in vitro* neutralization of merozoites because the CSF samples obtained (mixture of antibodies) from horses with EPM not only contained antibodies to *Sarcocystis neurona* but also other Sarcocystis species as horses infected with both *Sarcocystis neurona* and other Sarcocystis species . Thus the prior art teaches a method of inhibiting merozoites (neutralize parasite merozoites that causes *S.neurona* ) using a mixture of antibodies to surface antigens 30KD and 16 KD etc and warrants further investigation as candidate antigens for inclusion in vaccines, treating or preventing against *S.neurona* infection (see 1837, right column, last paragraph).

Liang et al 1997 (see page 65, left column, last paragraph) teach purified 30 KD and 19 KD (i.e. 16KD $_{+/-4)}$) antigens from *S.neurona* merozoites by using infected horse serum. Further, the prior art teaches high-resolution purification of these proteins by a combination of SDS-PAGE, isoelectric focusing and membrane blotting (see figure 3). However, the prior art does not teach a method of inhibiting *S. neurona* infection comprising providing a mixture of monoclonal antibodies. Harlow and Lane teach monoclonal antibodies and polyclonal antibodies (see chapter 5 and 6) by immunizing animals against a given antigen, preparing hybridoma to obtained monoclonal antibodies, useful for various immunological purposes.

It would have been prima facie obvious to one, having ordinary skill the art at the time the invention was made to make either monoclonal or polyclonal antibodies to merozoite surface antigens including 16KD and 30KD because Liang et al taught antibodies to surface antigen can inhibit infection in neutralization assays. Further, the art suggests monoclonal antibodies are often used to study parasite (page 1837, last paragraph) proteins and humoral responses play an essential role in blocking this migration and specific cytotoxic T cells are ineffective in attacking merozoite migration to the central nervous system in the blood stream (page 1837, left column, third paragraph) in EPM. Therefore, an artisan of ordinary skill would have been motivated to use readily available and purified surface antigens (Liang et al 1997) from merozoites including 16KD and 30 KD as disclosed by the prior art Liang et al 1998 or Liang et al 1997 with a reasonable expectation of success for raising antibodies (monoclonal/ polyclonal antibodies) by using well established immunization procedures (chapter 5), hybridoma technology (chapter 6) as taught by Harlow and Lane 1986 and using mixture of polyclonal antibodies to 30KD and 16KD or mixture of monoclonal antibodies to 30KD and 16KD in a method for inhibiting *S.neurona* infection in an equid infected with *S.neurona* infection by inoculating mixture of antibodies s because Liang et al 1998 clearly taught and suggested that humoral immunity to *S.neurona* infection is important (see figure 2, page 1836 under discussion ) in clearing *S.neurona* merozoites in an *invitro* method (neutralization) Further, the art clearly suggests that not all antibodies generated during infection will neutralize the merozoites and extended exposure to antiserum (see Liang et al 1998, page 1837, 2nd paragraph, left column in particular) is important (i.e., providing/inoculating infected horses with antibodies). The claimed invention is prima facie obvious over Liang et al 1998 or Liang et al 1997 and each in view of Harlow and Lane 1986 (chapters 5 and 6) absent any convincing evidence to the contrary.

***(10) Response to Argument***

Appellant's arguments filed on 5/ have been fully considered but they are noted deemed to be persuasive.

Appellant states that according to See M.P.E.P. 2141, I and M.P.E.P. 2141.02 , all of the claim limitations must be taught or suggested by the prior art to establish prima facie obviousness of a claimed invention and all limitations in a claim must be considered in judging the patentability of that claim against the prior art. Liang et al. 1998, Liang et al. 1997, and Harlow and Lane, either taken alone or in combination, do not show or suggest a method of treating an equid infected with *S.neurona* comprising (a) providing a mixture of antibodies against a 16 kD antigen and a 30 kD antigen, both of which are specific to *S. neurona*, wherein the antibodies are selected from the group consisting of polyclonal antibodies and monoclonal antibodies in a pharmaceutically acceptable carrier; and (b) inoculating the equid with the antibodies in the carrier to treat the equid. Neither do the cited references show or suggest the mixture of antibodies in a pharmaceutically acceptable carrier.

Contrary to the assertion of Appellant Liang et al1998 not only identified 16KD and 30KD merozoites surface antigens but also taught a method of inhibiting merozoite ( invitro neutralization assay ) activity using mixture antibodies to 16 kD antigen and a 30 kD in serum samples obtained from horses infected with *S.neurona* merozoites (figure 2, group 2, 3 and 4 ). Liang et al also established that antibodies to 16KD and 30 KD antigen neutralize the merozoite infection and antibody inhibitory activity was correlated with the immunoblot analysis. However, no activity was correlated in sera obtained from horses with EPM (see figure to N1-N6) with 30KD because antibodies to 30KD are not specific to *S.neurona* because sera obtained from horses with EPM also infected with other Sarcocystis species. Thus the prior art

clearly taught that mixture of antibodies (present in serum samples) to 16KD and 30 KD antigens neutralized the merozoite infection . Although Liang's results showed that antibodies to 30KD were not specific to *S.neurona* , Liang identified the problem that sera obtained from horses with EPM contained antibodies to other Sarcocystis species. Liang has provided a clear motivation that antibodies that are specific antibodies to 16KD and 30KD antigens that distinguish the EPM caused by *S.neurona* infection and EPM caused by other Species of Sarcocystis are critical in neutralizing the infection. Thus, the prior art not only taught a method of inhibiting merozoite infection but also identified specific antibodies to 30KD antigen are important in diagnosing EPM caused by *S.neurona* infection. Therefore, it is obvious to one of the ordinary skill in the art to make antibodies to merozoite surface antigens and mixing them together for treating horses because Liang et al clearly established that mixture antibodies to 30KD and 16KD neutralize the merozoites in an invitro method. Thus, the examiner has clearly established a prima facie obvious over Liang et al 1998 in view of Harlow and Lane by combining the teachings of the prior arts to produce the claimed invention. Thus motivation for combining the prior art references resides in the teachings of Liang et al 1998 itself.

Appellant states (page 8 through page 9, first 3 lines) that Liang et al concluded that no inhibitory activity of antibody to 30 KD antigen was correlated with band pattern and this can clearly seen with sample N6. Therefore, a person skilled in the art would not be motivated to pursue the claimed method.

The examiner disagrees with the appellant for the following reasons:

First Liang et al in figure 2 samples group 2-4 clearly demonstrated that there is a correlation between inhibitory activity and band pattern when serum samples obtained from horses infected with *S.neurona* in an *invitro* method of inhibiting merozoite invasion. Therefore, this is a clear indication for a person skilled in the art to be motivated to use Liang's method of

inhibiting merozoite invasion in a method to treat the horses infected with *S.neurona* as claimed because merozoites are known to spread the infection.

Second, appellant's method is for treating *S.neurona* infection but not a method of treating EPM disease as appellant arguing. Additionally, the sample N6 (CSF sample) is from horses with EPM and such horses not only infected with *S.neurona* but also other Sarcocytis. Therefore, Liang et al concluded specific antibodies to 30KD antigen are required to identify EPM caused by *S.neurona* in horses.

With respect to Liang et al 1997, 30KD and 19KD antigens were purified from merozoites and have been shown to be reactive to infected horse sera. In this reference, the motivation for making antibody to surface antigens 30 KD or 19KD (in consideration of the discrepancies often encountered in the art between protein molecular weights when determined by different methods, 19KD antigen is considered as 16KD +/- 4) is implicit as one of ordinary skill in the art of Parasitology knows how to make monoclonal or polyclonal antibodies for target surface antigens of merozoites.

The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art . In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). The examiner has established a prima facie case of obviousness over Liang 1998 in view of Harlow and Lane or Liang 1997 in view of Harlow and Lane as explained above .

Appellant cites the recent supreme court decision *KSR Int'l Co. v.Teleflex Inc.,* No. 04-1350, slip op. at 14, 15 (U.S. April 30, 2007) and states that Liang et al 1998 references combined or modified does not render the resultant combination obvious unless the prior art

also suggests the desirability of the combination. In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). None of the cited references would motivate a person of skill in the art to combine the teachings of the cited references.

The examiner disagrees with the appellant because it is noted that Liang's teachings for the first time brought the attention to one skilled in the art that mixture of antibodies present in serum samples obtained from horses infected with *S.neurona* infection and recognized specific antibodies to 16KD and 30KD antigens are important to neutralize the merozoites. Therefore, taken together with Liang's teachings and recent decision on KSR Int'l Co. v.Teleflex Inc., No. 04-1350, slip op. at 14, 15 (U.S. April 30, 2007, one skilled in the Parasitology art immediately understands that this is an important to produce specific polyclonal or monoclonal antibodies to 16KD and 30KD antigens to treat equid infected with *S.neurona* infection .The art clearly taught that merozoites are neutralized with specific antibodies and thus stop the invasion of merozoites not only in horses infected with *S.neurona* infection but also to stop infection spreading to central nervous system resulting the EPM disease. As explained above mixture of specific antibodies to surface antigens 30KD, 16KD are important targets for neutralizing *S.neurona* infection. Therefore, this reference provides clear motivation to the claimed method.

Appellant is misinterpreting the Liang's work as neutralization assays showed differential inhibitory activities. Liang et al established that antibodies to 16KD and 30KD antigen neutralize the merozoite infection and antibody inhibitory activity was correlated with the immunoblot analysis (see figure 2, samples 31-56) when serum obtained from horses infected with *S.neurona* infection . However, no inhibitory activity was correlated with antibodies 30KD antigen when CSF samples obtained from horses with EPM disease because horses with EPM disease are infected with other *Sarcocystis* species. Thus the prior art clearly taught that horses infected with *S.neurona* contain mixture of antibodies including to 16 KD and 30KD antigens

that stop the merozoite invasion . In addition, the art also recognized the problem that EPM disease is caused by other *Sarcocystis* species because it contains heterogeneous antibodies to 30KD antigen and therefore, there is a need for making specific (monoclonal or polyclonal) antibodies to *S.neurona* antigens 16KD and 30KD to specifically diagnose EPM disease. Therefore, it is obvious to one of the ordinary skill in the art to make specific antibodies to *S.neurona* merozoite surface antigens 30KD and 16kD and use them together to treat horses because the art clearly established antibodies to cell surface antigens neutralize the parasites because the art recognized the importance of humoral antibody in neutralizing the parasites. Thus, the examiner has clearly established a prima facie obvious over Liang et al 1998 in view of Harlow and Lane by combining the teachings of the prior arts to produce the claimed invention. Thus motivation for combining the prior art references resides in the teachings of Liang et al 1998.

Appellant states that Liang et al in 1997 teach an example for the method of purification of proteins and does not teach or suggest that Sarcocystis neurona proteins are important. The examiner disagrees with the Appellant because one skilled in the art of immuno Parasitology knows the importance of specific antibodies to surface proteins are useful to treat or cure the infection caused by *S.neurona*. Thus, the implicit teaching of Liang et al 1998 and 1997 is sufficient enough for one skilled in the art to use specific antibodies for treating an equid.

Appellant states that there is no art, which suggests making antibodies to these antigens, and the motivation for combining with Liang 1998 or Liang 1997 with Harlow and Lane to produce the Appellant's claimed method is a hindsight rejection, which is impermissible.

The examiner disagrees with the Appellant again because the prior art teaches antibodies to merozoite surface proteins have therapeutic value as antibodies neutralized the parasites. The general techniques for making monoclonal antibodies are routine in the art.

Liang's 1997 and 1998 teachings are sufficient to support the examiner's position. Therefore, one skilled in the Parasitology art immediately understands that specific polyclonal or monoclonal antibodies to *S.neurona* have therapeutic value. Further, the present specification on page 27 and 34 cites that the techniques for making monoclonal antibodies are well known in the art including the method of Harlow and Lane as applied by the examiner. Thus, the examiner has clearly established a prima facie case of obviousness over Liang et al 1998 in view of Harlow and Lane or Liang et al 1997 in view of Harlow and Lane by correctly combining the teachings of the prior art to produce the claimed invention. It is noted that board affirmed the examiner's rejection under 35 U.S.C 103 ( a) over combination of Liang 1998 or Liang 1997 and Harlow in a related Appeal Number 2004-1976, U.S.S.N. 09/669,843 . That appeal contained a claim to a monoclonal mixture comprising an antibody that selectively binds to 16kD and 30KD antigen of *S.neurona*. Thus, it appears that this is not an improper rejection based upon the teachings and suggestions from the prior art.

11. For the above reasons, it is believed that the rejections should be sustained.

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER

Respectfully submitted,
Padma Baskar
Padma Baskar Ph.D.
Examiner, Art Unit 1645

Conferees
Jeffrey Siew, SPE, Art Unit 1645
Larry Helms, SPE , Art Unit 1643

/Larry R. Helms/
Supervisory Patent Examiner

MCLEOD MOYNE & REILLY, P.C.
2190 COMMONS PARKWAY
OKEMOS MI 48864